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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,150	02/17/2004	David Munn	NEWL-005/02US 142996-2008	1273

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EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	PAPER NUMBER
1628	
MAIL DATE	DELIVERY MODE
07/16/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/780,150	MUNN ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-7,10,17,18,20-24,26,27,43,97,99-103,105,106,134 and 135* is/are pending in the application.

4a) Of the above claim(s) *1,5-7,10,17,18,20-24,26,27,43,97 and 102* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,99-101,103,105,106,134 and 135* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/1/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/17/2010 has been entered.

Response to Arguments

2. Applicants' arguments, filed 5/17/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

3. Applicant's arguments, see pp. 7-8, filed 5/17/2010, with respect to the rejection under 35 USC 102 have been fully considered and are persuasive. The rejection of claims 2, 98-101, 103, 105-106 being anticipated by Van Den Eynde et al. (WO 00/66764) has been withdrawn.

The amended claim language, "consisting of 1-methyl-D-tryptophan" now requires the D isomer, but excludes the D/L racemic mixture, which is taught by Van Den Eynde. Van Den Eynde does not teach compositions being administered that only contain the D isomer and pharmaceutically acceptable excipients.

4. Applicant's arguments with respect to the rejection under 35 USC 112, 1st paragraph have been fully considered but they are not persuasive:

Claims 2, 99-101, 103, 105-106 and 135 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for delaying the progression of a specific melanoma and a specific lung tumor by administering a composition consisting of 1-methyl-D-tryptophan and one or more pharmaceutically acceptable excipients, does not reasonably provide enablement for delaying the progression of other tumors by administering 1-methyl-D-tryptophan without an additional chemotherapeutic agent.

The rejection is maintained and applied to new claim 135 for the reasons of record, and the reasons that follow.

Applicant argues that the data presented in Hou and the Mautino Declaration demonstrate delayed tumor progression in a melanoma and lung cancer model after administration with 1-methyl-D-tryptophan alone in the absence of further administration of any chemotherapeutic agent; that the fact that the claimed method has worked in two very different cancers fully enables one skilled in the art to be able to practice the invention free of undue experimentation. As was pointed out previously, the record indicates that the claimed compound demonstrates a delay in the progression of a single melanoma cell line that has a large expression of IDO, supporting a delay in the progression of an IDO-expressing melanoma cell line; the declaration data also demonstrated that in a single lung cancer line, LLC, mice implanted with these tumors had a few days extended lifespan compared to control animals. The record does not

make clear whether or not LLC is IDO expressing, as is the case for the melanoma cell line of the Hou article. This point is important with respect to the demonstrated IDO inhibition activity. In summary, one cell line with expression of IDO and a second cell line which may or may not express IDO have demonstrated delay of tumor progression with the claimed compound.

However, in contrast to this, the claimed compound did not have activity in B16F10 cell lines, except when cyclophosphamide was also administered, which is presented in the instant specification, Figure 11D, and in the Hou article, Appendix B of the Mautino Declaration, filed 9/14/2009. The Prendergast Declaration, filed 10/14/2008 demonstrates that in a colon cancer cell line, 1MT (the racemic mixture of the instantly claimed compound) had no effect on tumor volume, except when cyclophosphamide was also administered (Exhibit B). The Hou article in Appendix B of the Mautino Declaration further demonstrates that The D/L racemic appears to have no effect on orthotopic 4T1 tumors in the absence of cyclophosphamide (a breast cell line; see Figure 2 A); a less immunogenic parental tumor B78H1 (a B16 melanoma subline) also had no effect when D-1MT was administered (Hou, Figure 5C, right). This evidence indicates that only two cancer cell lines have demonstrated efficacy when the claimed compound is administered without an additional chemotherapeutic agent to a mouse with the implanted cancer. In contrast, there are four examples for which the elected compound was not effective, when administered as the only active agent. This is reflective of the complexity and unpredictability in the field of cancer therapy. While a drug may have activity in tumor development delay in one or two cancer types, based

on the current unpredictability in this field, it is unlikely that this can be extrapolated to other cancer types, and especially for those that do not express IDO, which is substantiated by the data from the cell lines tested.

Applicant argues that the Examiner has not shown what type of undue experimentation would be necessary for one of ordinary skill in the art to apply the claimed method to cancers other than melanoma and lung tumors, that one of ordinary skill in the art would not be unduly burdened by applying the methods of the current invention, which have proven to be useful in two very different cancers, to any cancer. This is not persuasive. The point is that the state of the art reflects unpredictability in extrapolating data from two specific cancer lines to other cancer types, especially when the same drug is applied clinically. It is unlikely that the claimed method will be effective in other cancer types when the recited compound is administered as the only active agent, i.e., without the administration of a second active chemotherapeutic agent. Since it is unlikely to be effective, it leads to the conclusion that it would require undue experimentation. It is precisely the point that is is not clear what approach could be used to accomplish the recited method in the full scope of the claims, with the exception of a combination therapy, where a second drug, known to be active for a given cancer type, is also administered along with the 1-methyl-D-tryptophan containing composition. However, this embodiment is not required by the elected specie under examination, and is not recited by any claim under examination. Apart from this embodiement, and apart from the application of the method to one of the two types of cancer for which activity has been presented on the record (i.e., the tumor types recited in claim 134), other

embodiments within the scope of the instant claims are unlikely to achieve the recited delay in the progression of the cancer type.

Based on Van Den Eynde et al. (WO 00/66764; 2000; cited in prior Office Action), which has been discussed in the record, cells that express IDO might also be targeted, and have a little higher likelihood of responding to the instantly claimed method. However, none of the instant claims recite or are limited to any such IDO expressing cancer type.

Applicant argues that 1-methyl-D-tryptophan is not necessarily targeting inhibition of IDO within the tumor cell itself, but rather is targeting inhibition of the effects of IDO activity within cells of the hosts immune system, such as IDO+ dendritic cells; that it does not matter whether or not a tumor cell expressed IDO. If this general mechanism were the case, then B16F10, the colon cancer of the Prendergast Declaration, the 4T1 breast cell tumor and the B78H1 cancers should each have been responsive to treatment with the claimed 1-methyl-D-tryptophan, without cyclophosphamide. In contrast to this argument, the above referenced data demonstrate that this is not the case; the growth of these cell lines were not responsive to 1-methyl-D-tryptophan when the compound alone was administered, without cyclophosphamide.

5. Applicant's arguments, see p. 9, filed 5/17/2010, with respect to the rejection under 35 USC 112, 2nd paragraph have been fully considered and are persuasive. The rejection of claims 2, 98-101, 103, 105-106, 108, 124-127, 129 and 131-133 has been withdrawn.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 2, 99-101, 103, 105-106 and 134-135 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Den Eynde et al. (WO 00/66764; 2000; cited in prior Office Action); in view of Peterson et al. ("Evaluation of Functionalized-Tryptophan

Derivatives and Related Compounds as Competitive Inhibitors of Indoleamine 2,3-Dioxygenase"; 1994; Med. Chem. Res.; 3:531-544: Ids 5/3/2007 reference); and Karrer "Organic Chemistry" 1947; 3rd Ed., Elsevier Publishing Company, Inc., New York, pp. 94-105).

Van Den Eynde teaches methods for increasing T cell proliferation comprising administering a tryptophan-enhancing agent (Abstract). Suitable tryptophan-enhancing agents include inhibitors of indoleamine-2,3-dioxygenase (IDO) (page 1, lines 18-21). Preferred IDO inhibitors include 1-methyl-DL-tryptophan (page 2, lines 12-13 and page 6, line 30-31). The reference further teaches methods of treating cancer, expression of indoleamine 2,3-dioxygenase by the cancer cells indicates that the patient is a good candidate to be treated with an inhibitor of indoleamine 2,3-dioxygenase to increase the sysceptibility of the cancer cells to T cell attack (page 3, lines 30-33; page 18, lines 4-19 and lines 25-29). Two out of 12 human tumor cell lines were positive for IDO expression, including a melanoma cell line (p. 21, lines 25-27); the results suggest that certain tumors express IDO and thereby are capable of paralyzing the T cells that could otherwise attack them; these results suggest that IDO inhibitors could be used in ivov in patients bearing tumors that express IDO constitutively; thes patients are more likely to benefit from IDO inhibition in the framework of cancer immunotherapy, as their tumors, by expressing IDO constitutively, are capable of down regulating the tumoricidal effects of T cells which recognize the tumor (p. 22, lines 1-6). Van Den Eynde teaches a series of tumor cell lines expressing IDO, which include 27% of the melanoma cell lines and 42% of the Non-Small Cell Lung cancers tested (p. 24, Table I); in an example Fig 5

demonstrates reduction of tumor size and growth rate of a group of animals treated with 1-methyl-tryptophan in a group of mice injected with the lowest number of tumor cells, demonstrating that retarding of the development of tumor was observed for mice, suggesting that 1-methyl-tryptophan inhibits tumor growth and therefore may be useful in therapeutic treatment of tumors expressing IDO (p. 25, lines 14-19). Van Den Eynde teaches when administered in vivo, the compositions can be administered in preparations that contain carriers (excipients; p. 18, lines 20-23); oral administration (p. 18, line28); carriers such as Ringer's solution and isotonic sodium chloride solution (would form a solution; p. 20, lines 30-31); initial doses are followed by higher doses under certain circumstances (this would be at least 2 lower doses, from the plural form of the word, followed by at least 2 higher doses; followed by indicates a time interval, which meets the limitation of claim 105; p. 19, lines 18-21). An amount effective to inhibit IDO expression and retard the growth of a tumor is taken to meet the effective amount limitation of the instant claims.

Van Den Eynde does not teach administration of a composition that consists of only 1-methyl-D-tryptophan; i.e., all of the compositions taught by Van Den Eynde contain the racemic D/L mixture.

Peterson teaches the stereochemical requirements of the active site of human monocyte/macrophage IDO were probed by assays of both antipodes of 1-methyltryptophan 3a/3b; the L-isomer of 1-methyltryptophan 3a (62.9% inhibition, Ki = 34 μM) was found to be significantly more active than its antipode 3b (11.6% inhibition) (abstract). Peterson establishes that both L- and D-stereoisomers are active inhibitors

of IDO. Taken together with Van Den Eynde, leads to an expectation that delay of tumor growth is expected for each of these isomers if administered individually in subjects with tumors that constitutively express IDO, such as the melanoma cell line discussed by Peterson.

Karrer teaches the physiological properties of two antipodes (stereoisomers) can differ considerably, e.g., l-adrenaline is much more pharmacologically active than d-adrenaline; the cause of the different physiological behaviour of antipodes lies in the fact that many constitutents of cells within the organism with which the substances react are themselves asymmetric (p. 99, 5th paragraph). Karrer establishes that there is an expectation that one stereoisomer will be more effective in pharmacological activity, such as anti-cancer therapy using an IDO inhibitor compound.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the Van Den Eynde method of administering 1-methyl-tryptophan to a subject with an IDO expressing melanoma tumor to administering a pharmaceutical composition consisting of 1-methyl-D-tryptophan and an excipient to the same subject, with a reasonable expectation of activity. The motivation would have been to isolate each isomer to determine the efficacy for each in the method taught; the activity of both compounds based on Peterson would have also lead to an expectation that the D-isomer would have been activity for the same purpose taught by Van Den Eynde. Furthermore, by utilizing each stereoisomer, it would have been determined which of the compounds is more active for the purpose of delaying the growth of the

tumor cell, a process suggested by Karrer to have different outcomes for the two compounds.

According to In re Adamson and Duffin, 128 USPQ 233 (CCPA 1960), the court determined that even when laevo-isomers have substantially higher spasmolytic activity that either the dextro-isomer or the racemic mixture, as well as having only slightly higher toxicity than the same quantity of the racemate, facts present on the record based on an affidavit submitted, when considered with the 2nd edition of Karrer, that teaches fundamentals of optical activity and stereo-isomerism, the physiological properties of the two antipodes [stereo-isomers] can differ considerably, where several examples of differing physiological effects are given, and the cause of the different physiological behavior lies in the fact that many constituents of cells within the organism with which the substances react are themselves asymmetric. It was the court's opinion that the compounds are unpatentable; that the Karrer teachings would suggest to one skilled in the art that the racemates of the Adamson references may be resolved into their laevo- and dextro-isomers, and appellants in following the teachings of the cited prior art have done no more than the obvious. With respect to the argument of the l-isomer's superior spasmolytic activity, the court determined that in establishing that fact experimentally appellants have done no more than is suggested by the prior art and have ascertained no more than what would be expected by one skilled in the art, i.e., the activities are different.

The same fact pattern applies to the instant case; the prior art teaches the racemic mixture for the same purpose of treating IDO expressing melanoma in a

subject. The fact that the D-isomer has been determined to be more effective than the L-isomer at stimulation of T-cells, based on Figure 10 and a slight improvement in the length of survival when the D-isomer is coadministered with a second therapeutic agent, as compared to the racemic mixture and the L-isomer, according to Hou, Figure 6A, is according to Adamson, obvious over the references, where applicant has done what is suggested by the prior art.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571) 272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Examiner, Art Unit 1628